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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 09/981,915 | 10/16/2001 | Avi J. Ashkenazi | GNE.2630P1C12 | 8309 |

7590 06/20/2005

Ginger R Dreger
Heller Ehrman White & McAuliffe LLP
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Menlo Park, CA 94025

| EXAMINER | |
|---|---|
| BLANCHARD, DAVID J | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1642 | |

DATE MAILED: 06/20/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/981,915 | ASHKENAZI ET AL. | |
| | Examiner | Art Unit | |
| | David J. Blanchard | 1642 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *58-70* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *58-63 and 66-70* is/are rejected.

7)☒ Claim(s) *64 and 65* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *16 October 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *2/21/02; 5/6/02*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *Exhibit A*.



PD

## DETAILED ACTION

1. Claims 1-57 are canceled.

2. Claims 58-70 are pending and under examination.

### *Information Disclosure Statement*

3. The information disclosure statement submitted on 06 May 2002 has been considered by the examiner. However, since the Blast results cited therein are not true publications with a publication date, they are not fully in compliance with 37 CFR 1.97 and thus they will not be printed on the face of the patent issuing from this application.

### *Specification*

4. The disclosure is objected to because of the following informalities:

a. The ATCC address on page 372 needs to be updated to:

10801 University Boulevard, Manassas, VA 20110-2209.

b. The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code on page 311, line 33. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

Appropriate correction is required.

*35 U.S.C. § 112, Second Paragraph*

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

6. Claims 58-63, 66-67 and 69-70 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. Claims 58-63, 66-67 and 69-70 comprise the limitations that the claimed protein comprises an "extracellular domain" optionally lacking its associated signal peptide. These limitations are indefinite because neither the figure (figure 222) nor the specification define or teach the metes and bounds of the extracellular domain. Further, if the protein has an extracellular domain, the recitation of "extracellular domain"..."lacking its associated signal sequence" is indefinite as a signal sequence is not generally considered to be part of an extracellular domain, as signal sequences are cleaved from said domains in the process of protein production in the cell. It is noted that Figure 222 provides no written description of the extracellular domain.

b. Claim 70 is indefinite for reciting "epitope tag" because the exact meaning of the phrase is not clear. Does the phrase mean an "epitope" where and antibody binds or a tag that allows for purification that is an amino acid sequence that does not require binding to an antibody, or some other tag?

*Claim Rejections - 35 USC § 112*

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 58-62 and 69-70 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contain subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

The claims are drawn to polypeptides having at least 80% sequence identity with a particular disclosed sequence. The claims do not require that the polypeptide possess any particular biological activity, nor any particular conserved structure, or other disclosed distinguishing feature. Further, the claims encompass polypeptides having at least 80% amino acid identity with the extracellular domain of SEQ ID NO:523. Thus, the claims are drawn to a genus of polypeptides that are defined only by sequence identity and may have very different structures and functions.

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of compete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. In this case, the only factor present in the claim is a partial structure in the form of a recitation of percent identity. There is not even identification of any particular portion of the structure that must be conserved. Accordingly, in the

absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus.

*Vas-Cath Inc. v. Mahurkar*, 19USPQ2d 1111, clearly states "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116). As discussed above, the skilled artisan cannot envision the detailed chemical structure of the encompassed genus of polypeptides, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddles v.Baird*, 30 USPQ2d 1481, 1483. In *Fiddles v. Baird*, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class. The specification provided only the bovine sequence.

Therefore, only isolated polypeptides comprising the amino acid sequence set forth in SEQ ID NO:523, but not the full breadth of the claim meets the written description provision of 35 U.S.C. § 112, first paragraph. Applicant is reminded that

Vas-Cath makes clear that the written description provision of 35 U.S.C. § 112 is severable from its enablement provision (see page 1115).

9. Claims 58-63 and 68-70 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The specification is objected to under 35 U.S.C. § 112, first paragraph, as failing to provide an adequate written description of the invention and failing to provide an enabling disclosure without complete evidence either that the claimed biological materials are known and readily available to the public or complete evidence of the deposit of the biological materials.

The specification lacks complete deposit information for the deposit of the cell line containing cDNA deposited under ATCC accession No. 209487. It is not clear that the cDNA deposited as ATCC no. 209487 is known and publicly available or can be reproducibly isolated from nature without undue experimentation or is the same as SEQ ID NO:522 or contains additional sequences in addition to SEQ ID NO:522.

Applicant's referral to the deposit of the cDNA on pages 372-374 of the specification is an insufficient assurance that the required deposit has been made and all the conditions of 37 CFR 1.801-1.809 met.

If the deposit is made under the provisions of the Budapest Treaty, filing of an affidavit or declaration by applicant or assignees or a statement by an attorney of record

who has authority and control over the conditions of deposit over his or her signature and registration number stating that the deposit has been accepted by an International Depository Authority under the provisions of the Budapest Treaty and that all restrictions upon public access to the deposited material will be irrevocably removed upon the grant of a patent on this application. This requirement is necessary when deposits are made under the provisions of the Budapest Treaty as the Treaty leaves this specific matter to the discretion of each State.

If the deposit is not made under the provisions of the Budapest Treaty, then in order to certify that the deposits comply with the criteria set forth in 37 CFR 1.801-1.809 regarding availability and permanency of deposits, assurance of compliance is required. Such assurance may be in the form of an affidavit or declaration by applicants or assignees or in the form of a statement by an attorney of record who has the authority and control over the conditions of deposit over his or her signature and registration number averring:

(a) during the pendency of this application, access to the deposits will be afforded to the Commissioner upon request:

(b) all restrictions upon the availability to the public of the deposited biological material will be irrevocably removed upon the granting of a patent on this application:

(c) the deposits will be maintained in a public depository for a period of at least thirty years from the date of deposit or for the enforceable life of the patent of or for a period of five years after the date of the most recent request for the furnishing of a sample of the deposited biological material, whichever is longest; and

(d) the deposits will be replaced if they should become nonviable or non-replicable.

If a deposit is made after the effective filing date of the application for patent in the United States, a verified statement is required from a person in a position to corroborate that the biological material described in the specification as filed is the same as that deposited in the depository, stating that the deposited material is identical to the biological material described in the specification and was in the applicant's possession at the time the application was filed.

Applicant's attention is directed to In re Lundak, 773 F.2d. 1216, 227 USPQ 90 (CAFC 1985) and 37 CFR 1.801-1.809 for further information concerning deposit practice.

10. Claims 58-62 and 69-70 are rejected under 35 U.S.C. 112, first paragraph, because the specification, were it enabling for an isolated polypeptide comprising SEQ ID NO:523, would still not reasonably provide enablement for polypeptides having at least 80% amino acid sequence identity to SEQ ID NO:523. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is undue include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples,

6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

The claims are drawn to a polypeptide having at least 80% amino acid sequence identity to the polypeptide comprising SEQ ID NO:523 or the extracellular domain thereof both referred to as PRO337, optionally lacking its associated signal peptide. There is no functional limitation in the claims. Applicants have taught the polypeptide of SEQ ID NO:523, as well as the putative signal sequence (see Figure 222). However, Applicants provide little or no guidance beyond the mere presentation of sequence data to enable one of skill in the art to determine, without undue experimentation, the positions in the protein that are tolerant to change and the nature and extent of changes that can be made in these positions. Applicants have not asserted any activity for polypeptides comprising SEQ ID NO:523. The polypeptide variants could have structures and functions that are very different from the polypeptide of SEQ ID NO:523. In addition, because there is no activity disclosed for the PRO337 polypeptide, there would be no means for predicting or identifying other polypeptides that would have a similar activity.

The problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. While it is known that many amino acid substitutions are generally possible in any given protein, the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of

success are limited. Certain positions in the sequence are critical to the protein's structure/function relationship, such as various sites or regions directly involved in binding, activity, and in providing the correct three-dimensional spatial orientation of binding and active sites. Particular regions may also be critical determinants of antigenicity. These regions can tolerate only relatively conservative substitutions or no substitutions (see Bowie et al. (1990), Science 247:1306- 1310, especially p. 1306, column 2, paragraph 2; Wells (1990), Biochemistry 29: 8509-8517; Ngo et al. (1994), The Protein Folding Problem and Tertiary Structure Prediction, Merz et al., eds., Birkhauser, Boston, pp. 492-495).

Due to the large quantity of experimentation necessary to generate the large number of variants recited in the claims and screen the same for activity, the lack of direction/guidance presented in the specification regarding which structural features are required in order to provide activity, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art which establishes the unpredictability of the effects of mutation on protein structure and function, and the breadth of the claims which fail to recite any structural or functional limitations, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention.

***Priority***

Applicant claims priority to five previous applications in the preliminary amendment of 24 October 2003. The specification discloses that the claimed

polypeptides have patentable utility for the subject matter defined in claims based on the proliferation of rat utricular supporting cells assay (Example 116 at page 347), which was first disclosed in PCT/US99/05028 (WO 99/46281 see page 277), filed 3/8/1999 and the chondrocyte re-differentiation assay (Example 126 at page 351), which was first disclosed in PCT/US00/04341 (WO 00/53756), filed 2/18/2000. Therefore, the claims are granted the filing date of PCT/US99/05028, i.e., 3/8/1999 for purposes of applying the prior art.

***Claim Rejections - 35 USC § 102***

11. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

12. Claims 58-61 are rejected under 35 U.S.C. 102(b) as being anticipated by Struyk et al (The Journal of Neuroscience, 15(3):2141-2156, March 1995, Ids reference 12 filed 2/21/02).

The claims are drawn to an isolated polypeptide having at least 80% amino acid identity with the polypeptide of SEQ ID NO:523, optionally lacking its associated signal peptide (i.e., amino acids 1-28 of SEQ ID NO:523) or the amino acid sequence of the polypeptide encoded by the cDNA deposited under ATCC accession no. 209487 (i.e., SEQ ID NO:523).

Struyk et al teach an isolated polypeptide having at 91% amino acid identity with SEQ ID NO:523 and having 97% amino acid identity with the polypeptide of SEQ ID NO:523, lacking its associated signal peptide (i.e., full-length coding sequence) (see Figure 3 and the alignment attached to the back of this Office action as Exhibit A).

*Claim Rejections - 35 USC § 103*

13. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to

consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

14. Claims 58-61 and 69-70 are rejected under 35 U.S.C. 103(a) as being unpatentable over Struyk et al (The Journal of Neuroscience, 15(3):2141-2156, March 1995, Ids reference 12 filed 2/21/02) in view of Grose (U.S. Patent 5,710,248, issued 1/20/98).

Claims 58-61 have been described supra. Claims 69-70 recite a chimeric protein comprising a polypeptide that is at least 80% identical to SEQ ID NO:523 fused to an epitope tag.

Struyk et al have been described supra. Struyk et al do not teach a chimeric protein comprising an epitope tag. This deficiency is made up for in the teachings of Grose.

Grose teach a peptide tag for immunopurification and immunodetection.

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to have produced a chimeric polypeptide comprising the polypeptide taught by Struyk et al and a peptide tag.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have produced a chimeric polypeptide comprising the polypeptide taught by Struyk et al and a peptide tag because Grose teach insertion of a peptide tag into a protein facilitates the characterization of the protein (see column 1, lines 10-12). Thus, it would have been obvious to one of ordinary skill in the art to add a peptide tag to the polypeptide of Struyk et al for purification.

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

*Conclusion*

15. No claim is allowed. Claims 64-65 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

16. Fukushima et al (U.S. patent 6,664,383 B1) has been considered by the examiner, but not applied because the priority date of the instant claims is deemed to be 3/8/1999 (see "Priority" section above). Fukushima et al teach a polypeptide (SEQ ID NO:3) that is identical to SEQ ID NO:523 of the present claims.

17. Any inquiry concerning this communication or earlier communications from the examiner should be directed to David J. Blanchard whose telephone number is (571) 272-0827. The examiner can normally be reached at Monday through Friday from 8:00 AM to 6:00 PM, with alternate Fridays off. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew, can be reached at (571) 272-0787. The official fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR.

Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Respectfully,
David J. Blanchard
571-272-0827

JEFFREY SIEW
SUPERVISORY PATENT EXAMINER
6/10/05

Exhibit A

RESULT 1
I56551
neurotrimin - rat
C;Species: Rattus norvegicus (Norway rat)
C;Date: 26-Jul-1996 #sequence_revision 26-Jul-1996 #text_change 09-Jul-2004
C;Accession: I56551
R;Struyk, A.F.; Canoll, P.D.; Wolfgang, M.J.; Rosen, C.L.; D'Eustachio, P.; Salzer, J.L
J. Neurosci. 15, 2141-2156, 1995
A;Title: Cloning of neurotrimin defines a new subfamily of differentially expressed neu
A;Reference number: I56551; MUID:95198094; PMID:7891157
A;Accession: I56551
A;Status: preliminary; translated from GB/EMBL/DDBJ
A;Molecule type: mRNA
A;Residues: 1-344 <RES>
A;Cross-references: UNIPROT:Q62718; EMBL:U16845; NID:g755184; PIDN:AAA67445.1; PID:g755
C;Superfamily: carcinoembryonic antigen; carcinoembryonic antigen precursor amino-termi

Query Match 90.8%; Score 1639.5; DB 2; Length 344;
Best Local Similarity 92.9%; Pred. No. 2.5e-113;
Matches 312; Conservative 9; Mismatches 12; Indels 3; Gaps 1;

```
Qy         12 ISWAIFTGLAALCLF---QGVPVRSGDATFPKAMDNVTVRQGESATLRCTIDNRVTRVAW 68
              : |     ::   ||    |||||||||||||||||||||||||||||||||||||||||
Db          9 LPWKCLVVVSLRLLFLVPTGVPVRSGDATFPKAMDNVTVRQGESATLRCTIDNRVTRVAW 68

Qy         69 LNRSTILYAGNDKWCLDPRVVLLSNTQTQYSIEIQNVDVYDEGPYTCSVQTDNHPKTSRV 128
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db         69 LNRSTILYAGNDKWCLDPRVVLLSNTQTQYSIEIQNVDVYDEGPYTCSVQTDNHPKTSRV 128

Qy        129 HLIVQVSPKIVEISSDISINEGNNISLTCIATGRPEPTVTWRHISPKAVGFVSEDEYLEI 188
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        129 HLIVQVSPKIVEISSDISINEGNNISLTCIATGRPEPTVTWRHISPKAVGFVSEDEYLEI 188

Qy        189 QGITREQSGDYECSASNDVAAPVVRRVKVTVNYPPYISEAKGTGVPVGQKGTLQCEASAV 248
              |||||||||:|||||||||||||||||| ||||||||||||||||||||||||||||||
Db        189 QGITREQSGEYECSASNDVAAPVVRRVNVTVNYPPYISEAKGTGVPVGQKGTLQCEASAV 248

Qy        249 PSAEFQWYKDDKRLIEGKKGVKVENRPFLSKLIFFNVSEHDYGNYTCVASNKLGHTNASI 308
              |||||||:||||||:|||||||||||||||:| ||||||||||||||||||||||||||||
Db        249 PSAEFQWFKDDKRLVEGKKGVKVENRPFLSRLTFFNVSEHDYGNYTCVASNKLGHTNASI 308

Qy        309 MLFGPGAVSEVSNGTSRRAGCVWLLPLLVLHLLLKF 344
              ||||||||||:|||||||||:|||||||||||||||
Db        309 MLFGPGAVSEVNNGTSRRAGCIWLLPLLVLHLLLKF 344
```